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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,721	08/13/1999	JOHN HENRY KENTEN	IGN-2004	4071

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EXAMINER
ZEMAN, ROBERT

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/374,721	Applicant(s) KENTEN ET AL.	
	Examin r Robert A Zeman	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4-12-01, 7-30-01 and 1-4-02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-116* is/are pending in the application.

4a) Of the above claim(s) *1-81 and 101-116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-116* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendments and responses filed on 4-12-01, 7-30-01 and 1-4-02 are acknowledged. Claims 82, 83, 87-88, 91, 94 and 97-100 have been amended. Claims 1-81 and 101-116 remain withdrawn from consideration as they are drawn to non-elected inventions. Claims 82-100 are pending and currently under examination.

This application contains claims 1-81 and 101-116 drawn to an invention nonelected with traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections Withdrawn

The provisional rejection of claims 82-84, 88-91 and 96-100 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 76-79, 84-85, 87-90 and 93 of copending Application No. 09/026,276 is withdrawn. Cancellation of claims 76-79, 84-85, 87-90 and 93 in the copending application has rendered the rejection moot.

The rejection of claim 87 under 35 U.S.C. 112, second paragraph, for having insufficient antecedent basis for the limitation "ubiquitin moiety" is withdrawn in light of the amendment thereto.

The rejection of claims 91-92 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "physiological consequences of administration to the animal" is withdrawn in light of the amendment thereto.

The rejection of claims 91-92 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "substantially similar" is withdrawn in light of the amendment thereto.

The rejection of claims 82, 84, 88-89 and 97-100 under 35 U.S.C. 102(b) as being anticipated by Vannier et al. (Biochemistry, Vol. 35 pages 1358-1366, 1996-- IDS-6) is withdrawn in light of the amendment thereto.

The rejection of claims 82-100 under 35 U.S.C. 103(a) as being unpatentable over Vannier et al. (Biochemistry, Vol. 35 pages 1358-1366, 1996--- IDS-6) in view of van der Zee et al. (Vaccine Vol 13, No. 8, pages 753-758, 1995) is withdrawn in light of the amendment thereto.

The rejection of claims 82-100 under 35 U.S.C. 103(a) as being unpatentable over Vannier et al. (Biochemistry, Vol. 35 pages 1358-1366, 1996--- IDS-6) in view of van der Zee et al. (Vaccine Vol 13, No. 8, pages 753-758, 1995) is withdrawn. Applicant's arguments have been fully considered and deemed persuasive.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 82-89 and 95-100 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for **stimulating antibody production** in animals utilizing ubiquitin fused to gonadotropin releasing hormone (GnRH) or growth hormone, does not reasonably provide enablement for methods for stimulating **all immune responses** utilizing ubiquitin fused to **all self antigens** is maintained for reasons of record.

Applicant argues:

1. Applicants provide two independent working examples of the generation of an immune response to two different proteins (GnRH and growth hormone).

2. Applicants several working examples of ubiquitin fusion proteins (pX548, pX549 and pX552) that have self-epitopes fused at different positions within the ubiquitin molecule.

3. The determination of additional sites of epitope fusion that preserve the native secondary and tertiary structure of ubiquitin are within the ability of one of skill in the art.

4. Significant guidance is given in the Specification as to additional methods of enhancing the immunogenicity of the self epitope(s).

5. The field of immunogen synthesis is highly developed and other methods of experimentally inducing an immune response to a self-antigen are well known in the art, thus the selection of a self-epitope for incorporation into the ubiquitin fusion protein can be made by one of skill in the art by normal experimentation.

6. Applicants are not required to demonstrate that an invention is completely safe.

Applicant's arguments have been fully considered and deemed unpersuasive.

Applicant is correct when stating that the specification discloses two working examples of ubiquitin fusion proteins containing self-epitopes. However, as pointed out in the aforementioned rejection, these were the only examples of fusion proteins shown to induce any type of immune response. The specification is silent on what other, if any, immune responses said fusion proteins (or any other ubiquitin fusion protein) induced. Additionally, the GnRH or growth hormone self-epitopes were the only self-epitopes disclosed in the specification that induced **any** type of immune response, albeit antibody protein. Applicant cites fusion proteins pX548, pX549 and pX552 (pX546 is also disclosed in the Specification but is not cited by Applicant in his argument) as additional examples of self-epitopes that induced an "immune response". Said fusion proteins all contain variations of the GnRH epitope (see pages 51-52 and 54 of the Specification) and hence are merely a subset of GnRH containing fusion proteins. It should also be pointed out that pX548, pX549 and pX552 were only shown to induce antibody production and were not shown to induce any other type of immune response.

With regard to Applicant's assertion that "the field of immunogen synthesis is highly developed and other methods of experimentally inducing an immune response to a self-antigen are well known in the art", it should be pointed out that in order synthesize a given "immunogen" its sequence (either nucleic acid or amino acid) must be known. Therefore, since the Specification is silent on issue of said sequences, the selection of a self-epitope for incorporation in the ubiquitin fusion protein **cannot** be made by one of skill in the art by normal experimentation.

While Applicant is correct that they are not required to demonstrate that the claimed invention is completely safe, they are required to demonstrate that administration of their

invention provides a benefit to the subject to which it is being applied since the instant claims are drawn to the application of the claimed fusion proteins to an **animal** (including humans).

Consequently, since the aforementioned claims broadly encompass an infinite array of ubiquitin fusion proteins which contain an equally limitless number of self epitopes and the specification only discloses the fusion of GnRH to ubiquitin for the stimulation of a strong anti-GnRH response in order to suppress gamete maturation in both male and female pigs (see Examples 3-6 and 8-10) and the fusion of growth hormone in order to induce weight gain in pigs (see Example 7) the specification is **non-enabling** for the unlimited number of ubiquitin/self antigen fusion proteins which are encompassed by the scope of the claims. It should be noted that no material limitations for the ubiquitin fusion proteins have been recited in the claims while the claims encompass every conceivable structure (means) for achieving the stated property (result), The disclosed ubiquitin/GnRH and ubiquitin/growth hormone fusion proteins have specific characteristics and properties and hence, may differ structurally, chemically, physically, and functionally from other ubiquitin/self antigen fusion proteins. Finally, since the instant claims are all drawn to inducing an "immune response" to a self-antigen in an animal and the Specification has only demonstrated the induction of antibody production for the aforementioned fusion proteins (2) the specification is **non-enabling** for the induction of any other immune response other than antibody production. By application of the factors set forth in Ex parte Forman (230 USPQ546(Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which self-epitopes to be fused

to the ubiquitin to achieve the desired immune responses which are encompassed by the scope of the claims is practically infinite and the guidance provided by the specification is minimal. Coupled with the high degree of unpredictability of the art it would require undue experimentation to determine how to use all the possible ubiquitin/self antigen fusion proteins encompassed by the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 82, 84 and 97-99 are rejected under 35 U.S.C. 102(b) as being anticipated by Mouritsen et al. (WO 95/05849) is maintained for reasons of record.

Applicant argues:

1. The rejection is obviated by the amendment of the claims since said claims now recite that the immune response is directed toward a non-ubiquitin self-epitope.

Applicant's arguments have been fully considered and deemed non-persuasive.

Mouritsen et al. disclose the attachment of one or more T cell epitopes into the highly conserved self-protein ubiquitin (see pages 6-7). Mouritsen discloses 2 different ubiquitin fusion proteins: one containing the T-cell epitope ovalbumin (OVA 325-336) and the other containing

the T-cell epitope HEL (50-61). Injection of said fusion proteins into mice elicited a strong antibody response to the fusion protein. Moreover, Mouritsen et al. disclose, "the insertion of **one or more** foreign T cell epitopes induces a profound autoantibody response against said proteins" (see page 6, lines 31-33). Additionally, Mouritsen et al. disclose "the antibody response induced was not necessarily restricted to the inserted T cell epitopes" (see page 6, lines 33-35). Consequently, the disclosure of Mouritsen et al. anticipates all the limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 82-100 under 35 U.S.C. 103(a) as being unpatentable over Mouritsen et al. (WO 95/05849) in view of van der Zee et al. (Vaccine Vol 13, No. 8, pages 753-758, 1995) is maintained for reasons of record.

Applicant argues:

1. Mouritsen et al. teach the use of a fusion protein resulting from the insertion of a single copy of a T cell epitope internally into a single ubiquitin amino acid sequence to produce an immune response to ubiquitin.

2. van der Zee et al. teach the use of the highly immunogenic carrier P-fimbrae fused to a short, non-immunogenic GnRH decapeptide to generate an immune response to the GnRH peptide.

3. One of skill in the art would not predict with any degree of certainty the generation of an immune response to a self-epitope from immunization with ubiquitin fused to a self-epitope from the combined disclosures of van der Zee et al. and Mouritsen et al. since neither teach or suggest that ubiquitin has the ability to function as an immunological carrier for a heterologous epitope.

4. It is in **unexpected result** that ubiquitin has the ability to function as an immunological carrier for a heterologous epitope.

Applicant's arguments have been fully considered and deemed non-persuasive. As discussed above, Mouritsen et al. disclose "the insertion of **one or more** foreign T cell epitopes induces a profound autoantibody response against said proteins" (see page 6, lines 31-33). Additionally, Mouritsen discloses "the antibody response induced was not necessarily restricted to the inserted T cell epitopes" (see page 6, lines 33-35). van der Zee et al. teach a fusion protein comprising GnRH fused to fimbrae for the development of a contraceptive vaccine for use in domestic animals (see abstract and Figure 4 on page 757). van der Zee et al. also disclose that

GnRH is one of the most attractive vaccine components for the immunoneutralization because it is regarded as the key regulatory peptide in the reproduction cycle of mammals (see page 753, column 1). Finally, van der Zee et al. disclose that vaccination of female rats and bull calves with said fusion protein induced not only serological, but also pharmacological effects (see page 757) and as a consequence, that GnRH is a promising candidate for the use in the development of a contraceptive vaccine. Therefore, contrary to Applicant's assertion, would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify ubiquitin fusion proteins disclosed by Mouritsen et al. to use GnRH as the self epitope as disclosed by van der Zee et al. since GnRH is considered the pivotal regulatory peptide in mammalian reproduction and there is a demand for an effective, low cost means of controlling fertility in domestic animals. The resulting fusion protein would benefit from the increased stabilization, increased efficiency of translation and increased preservation of biological activity due to proper folding associated with ubiquitin fusion proteins, as well as the increased efficacy of associated with the use of the GnRH self antigen. Additionally, it should be noted that while Applicant is asserting unexpected results, no factual evidence of such results has been presented. Arguments and assertions do not substitute for factual evidence. Further, the prior art of record shows known advantages in using molecules as claimed.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on M-Th 7:30 am - 5:00 pm and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donna Wortman can be reached on (703) 308-1032. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Robert A. Zeman
May 16, 2002